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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,600	03/29/2002	Kei Yamana	Q69170	2994

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,600	YAMANA ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-6,8-18,20-23 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,19,24 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/29/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of group 4, Claims 7, 19, 24, 26 in Paper of 02/27/04 is acknowledged and entered.

Claims 1-26 are pending in the instant application and Claims1-6, 8-18, 20-23, 25 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Accordingly, group 4, claims 7, 19, 24, 26 are examined in the instant application.

OBJECTION

Claims 19, 24, 26 are objected to because claims 19, 24, 26 depend on non-elected claim 9.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 7, 19, 24, 26 are rejected under 35 USC 112, first paragraph.

Claims 7, 19, 24, 26 are drawn to a polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2.

The specification discloses that "substantially comprises" means that the polypeptide of the present invention, as long as it retains its function, may have

mutation such as substitution, insertion, or deletion in the amino acid sequence as set forth in SEQ ID NO:2 (p. 10, lines 21-28).

Claims 7, 19, 24, 26 encompass variants of SEQ ID NO:2, with unknown structure.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are clearly relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated,

does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of a polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2, per Lilly by structurally describing a

representative number said polypeptides, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2, required in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2 other than SEQ ID NO:2, nor does the specification provide any partial common structure of such a polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2, nor any physical or chemical characteristics of the polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2, other than SEQ ID NO:2, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polypeptide, SEQ ID NO:2, this does not provide a description of the polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2, that would satisfy the standard set out in Enzo.

The specification also fails to describe the polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2, by the test set out in Lilly. The specification describes only a single polypeptide, SEQ ID NO:2. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2, that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 7, 19, 24, 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, **does not reasonably provide enablement for a polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 7, 19, 24, 26 are drawn to a polypeptide encoded by a human gene that "substantially" comprises the amino acid sequence as set forth in SEQ ID NO:2.

The specification discloses that "substantially comprises" means that the polypeptide of the present invention, as long as it retains its function, may have mutation such as substitution, insertion, or deletion in the amino acid sequence as set forth in SEQ ID NO:2 (p. 10, lines 21-28).

The specification discloses mutants in which parts of the amino acid sequence of SEQ ID NO:2 are substituted, deleted or added. (p.13, second paragraph).

The scope of the claims 7, 19, 24, 26 encompasses numerous structural variants. Applicants have not shown how to make the claimed variants which are capable of functioning or have the properties of the polypeptide of SEQ ID NO:2, as that which is being disclosed.

The claims read on variant polypeptide of SEQ ID NO:2, wherein said polypeptide has any type of substitution besides conservative substitution, at any amino acid, throughout the length of the polypeptide, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes numerous structural variants. The specification and the claims do not provide any guidance as to which original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted in the polypeptide, so that the polypeptide could function as contemplated.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the variants of SEQ ID NO:2 would have properties related to that of SEQ ID NO:2. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology and that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the

substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification does not disclose how to make the variant polypeptides, such that they would function or have the properties as claimed.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is

known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability that the claimed variants would have the property or function of SEQ ID NO:2 , the lack of adequate disclosure in the specification on how to make such variants, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. Claims 19, 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:2, having an effect of in vitro inhibition of the formation of tube-like structure of human umbilical vein endothelial cells, **does not reasonably provide enablement for a "pharmaceutical composition"** comprising a polypeptide encoded by a human gene that substantially comprises the amino acid sequence as set forth in SEQ ID NO:2, or a polypeptide encoded by a human gene that substantially comprises the amino acid sequence as set forth in SEQ ID NO:2 "having an effect of inhibiting angiogenesis in vivo as contemplated". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 19, 26 are drawn to a pharmaceutical composition comprising a polypeptide encoded by a human gene that substantially comprises the amino acid sequence as set forth in SEQ ID NO:2, or a polypeptide encoded by a human gene that

substantially comprises the amino acid sequence as set forth in SEQ ID NO:2 having an effect of inhibiting angiogenesis.

The specification discloses that SEQ ID NO:2 (ChM1L) is expressed besides in the brain, the skeletal muscle, the whole rib, and the thyroid (p.16, second paragraph and figure 3(a)), but also expressed in the eyeball, a tissue that is resistant to vascular invasion. The specification discloses that these results suggest that SEQ ID NO:2 may be associated with Alzeihmer's disease, skeletal-related muscle diseases such as muscular dystrophy, thyroid-related diseases such as Basedow's disease, eyeball-related disease such as diabetic retinopathy, cartilaginous tissue-related diseases such as osteoarthritis, and rheumatoid arthritis, and angiogenesis-related diseases such as cancer (p. 16, last paragraph). The specification discloses that thus SEQ ID NO:2 are considered to be used as therapeutic agents for these diseases (p.16, last four lines bridging p.17).

The specification discloses that the claimed polypeptide inhibits the formation of tube-like structure of human umbilical vein endothelial cells in vitro, a test for angiogenesis, as compared to the control (Example 14 on pages 39-40)..

It is noted that inherent in a pharmaceutical composition is the in vivo use thereof.

It is further noted that a polypeptide encoded by a human gene that substantially comprises the amino acid sequence as set forth in SEQ ID NO:2 having an effect of inhibiting angiogenesis encompasses a polypeptide encoded by a human gene that

substantially comprises the amino acid sequence as set forth in SEQ ID NO:2 having an effect of inhibiting angiogenesis in vivo as contemplated.

One cannot extrapolate the teaching in the specification to the claims, because it is well known in the art that treating angiogenesis is unpredictable. For example, MSN Health News, 2000, pages 1-5, teaches that further study is needed to determine how effective cancer therapy will be to an angiogenesis inhibitor drug, such as endostatin, because response of different human cancer patients to endostatin is variable, wherein in most of the cases their cancer worsens, and at best the tumors do not get any bigger. MSN Health News further teaches that said cancer therapy in human patients does not reflect the impressive results from experiments using laboratory mice. In other words, not any angiogenic diseases would be effectively treated by an angiogenesis inhibitor drug. Thus based on the teaching in the art and the specification, one cannot predict that the claimed polypeptide would be effective for in vivo treating angiogenic diseases.

Further, one cannot extrapolate the in vitro inhibition of the formation of tube-like structure of human umbilical vein endothelial cells to treating angiogenesis in vivo, because in vitro assays cannot duplicate in vivo conditions, wherein in in vitro assays, the cells are constantly exposed to the claimed polypeptide, which is not the same as in vivo. A therapeutic polypeptide must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the target cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the in vitro assays, the claimed polypeptide is in contact with cells during the entire

exposure period. This is not the case *in vivo*, where exposure tat the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The polypeptide may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the protein and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the polypeptide may not otherwise reach the targert because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the polypeptide has no effect, circulation into the target area may be insufficient to carry the polypeptide and a large enough local concentration may not be established.

Given the unpredictability of treating angiogenic diseases, the lack of adequate disclosure in the specification on how to make such variants, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 102(e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 7, 19, 24, 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Baker et al, US 2003/0073129A1 or Eaton et al, US 2002/0119130A1.

Claims 7, 19, 24, 26 are drawn to:

1) A polypeptide encoded by a human gene that substantially comprises the amino acid sequence as set forth in SEQ ID NO:2 (claim 7), wherein said polypeptide is a membrane-bound form (claim 24),

2) A pharmaceutical composition comprising said polypeptide (claim 19), or

3) A polypeptide encoded by a human gene that substantially comprises the amino acid sequence as set forth in SEQ ID NO:2 having an effect of inhibiting angiogenesis (claim 26).

The specification discloses that "substantially comprises" means that the polypeptide of the present invention, as long as it retains its function, may have

mutation such as substitution, insertion, or deletion in the amino acid sequence as set forth in SEQ ID NO:2 (p. 10, lines 21-28).

Thus a sequence substantially comprises SEQ ID NO:2 encompasses SEQ ID NO:2 or variants thereof.

Claim 19 recites the claimed polypeptide, formulated as a pharmaceutical composition. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claims read on the ingredient per se, which is a polypeptide encoded by a human gene that substantially comprises SEQ ID NO:2.

Further, claims 24, 26 recite the claimed polypeptide having an effect of inhibiting angiogenesis could be reasonably interpreted as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claims read on the ingredient per se, which is a polypeptide encoded by a human gene that substantially comprises SEQ ID NO:2.

US 2003/0073129A1 or US 2002/0119130A1 teaches a sequence, SEQ ID NO:322 and SEQ ID NO:116, respectively, which is 100% similar to the claimed SEQ ID NO:2, from amino acid 1 to amino acid 371, as shown by MPSRCH sequence similarity search (MPSRCH search report, 2004, us-10-089-600-2.rapb, pages 1-3, 6-7).

The sequence taught by US 2003/0073129A1 or US 2002/0119130A1 seems to be the same as the claimed sequence.

Although the reference does not specifically teach that the polypeptide is membrane-bound. However, the claimed polypeptide appears to be the same as the

prior art polypeptide. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989)..

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

April 13, 2004